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Fat mass and obesity-associated gene polymorphisms do not affect metabolic response to hormone therapy in healthy postmenopausal women☆

Ramon B. Ramos [a,b], Gislaine K. Casanova [a,b], Poli M. Spritzer [a,b,c,*]

[a] Gynecological Endocrinology Unit, Division of Endocrinology, Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil
[b] National Institute of Hormones and Women's Health, CNPq, Porto Alegre, Brazil
[c] Laboratory of Molecular Endocrinology, Department of Physiology, Universidade Federal do Rio Grande do Sul (UFRGS), Porto Alegre, Brazil

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ABSTRACT

Objective: To determine whether fat mass and obesity-associated gene polymorphisms rs9939609 T>A and rs8050136 A>C or their haplotypes influence anthropometric and metabolic variables in recently postmenopausal women receiving hormone therapy.
Study design: In this randomized crossover study carried out in a university clinic, 86 postmenopausal women consulting for symptoms of estrogen deficiency were genotyped by real-time polymerase chain reaction for single nucleotide polymorphisms rs9939609 T>A and rs8050136 A>C of the fat mass and obesity-associated gene. Haplotypes were constructed from the combination of polymorphisms rs9939609 and rs8050136, and their frequencies were inferred using the PHASE 2.1.1 program. Participants were clinically evaluated before and after 6 months of hormone therapy to determine body mass index (current kg/m^2) and waist circumference, blood pressure, lipid profile (total cholesterol, HDL cholesterol and triglycerides) plasma glucose (oral glucose tolerance test), and insulin. Blood samples were also drawn for ultra sensitive C reactive protein. The lipid accumulation product index was calculated as (waist [cm] – 58) × triglyceride concentration (mmol/L). Non-normally distributed parameters were log10 transformed before statistical analysis. Measurements at baseline and at follow-up were compared with ANOVA for repeated measures. Data were considered significant at $P < 0.05$.
Results: In women with the homozygous polymorphic AA genotype of the single nucleotide polymorphisms rs9939609 and the wild AA genotype of the single nucleotide polymorphisms rs8050136, lipid accumulation product index and ultra sensitive C reactive protein were higher before hormone therapy in comparison with women with other genotypes from the same single nucleotide polymorphisms group. There was no worsening of any of the anthropometric or metabolic variables, and lipid accumulation product index improved slightly after hormone therapy in SNP rs9939609 ($P = 0.03$) and haplotype AAAA. No changes were observed after hormone therapy in SNP rs8050136.
Conclusions: The presence of fat mass and obesity-associated gene risk variants in healthy early postmenopausal women does not adversely affect their response to hormone therapy.

1. Introduction

In the postmenopausal period, women experience an exponential increase in the risk of cardiovascular disease, the leading cause of death in this population [1]. During the reproductive years, endogenous estrogens exert beneficial effects on endothelial function and lipids, and the estrogen deficiency that occurs after the menopause has been related to a worsening in the clinical and metabolic profile in this population. Studies have shown an increase in the incidence of diabetes, hypertension, and dyslipidemia, as well as increased risk for the metabolic syndrome, even after adjustment for confounding variables [2]. Deposition of abdominal fat is also increased as compared to peripheral fat [3]. Prospective randomized trials have shown that hormone therapy (HT) is not beneficial for primary or secondary cardiovascular prevention [4,5]. A recent analysis, however, indicates that HT may be safe for recently postmenopausal women in whom atherosclerosis is still not entirely established [6].

Recently, single nucleotide polymorphisms (SNPs) rs9939609 T/A and rs8050136 A/C of the fat mass and obesity-associated (FTO) gene have been linked to body mass index (BMI), risk of obesity, adiposity, metabolic syndrome and high cardiovascular risk in both men and women. A case–control study from the Women's Health

☆ This study was conducted at Hospital de Clínicas de Porto Alegre (HCPA), Porto Alegre, Brazil.

* Corresponding author at: Division of Endocrinology, Hospital de Clínicas de Porto Alegre, Rua Ramiro Barcelos 2350, Porto Alegre 90035-003, RS, Brazil. Tel.: +55 51 3359 8027; fax: +55 51 3359 8777.
E-mail address: spritzer@ufrgs.br (P.M. Spritzer).

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Initiative Observational Study, conducted with four ethnic groups, showed an association of polymorphisms rs9939609 and rs8050136 with BMI and waist circumference in white and Hispanic postmenopausal women, but no association was observed with obesity-related metabolic traits, including systolic blood pressure, diastolic blood pressure, plasma fasting insulin, glucose, and ultra sensitive C reactive protein (us-CRP), a reliable marker of cardiovascular risk [7]. In turn, we have recently shown an association of these FTO gene variants with the lipid accumulation product (LAP) index, which is also a marker of postmenopausal cardiovascular and metabolic risk [8]. LAP is based on a combination of two measurements: waist circumference and the fasting concentration of triglycerides. Studies have shown an association of LAP with cardiovascular risk factors and metabolic comorbidities in a healthy population [9,10]. There are, however, no studies in the literature evaluating whether the presence of FTO gene variants influences the effects of HT in postmenopausal women.

Therefore, the aim of the present study was to assess whether FTO gene polymorphisms rs9939609 T>A and rs8050136 A>C are associated with changes in anthropometric and metabolic variables and us-CRP levels in recently postmenopausal women receiving HT.

2. Materials and methods

2.1. Patients

This randomized crossover study was carried out with women consulting for climacteric symptoms at the Gynecological Endocrinology Unit in a university hospital (Hospital de Clínicas de Porto Alegre) in Brazil. Eighty-six postmenopausal women fulfilling the following inclusion criteria were consecutively enrolled: last menstrual period between 6 months and 3 years before the beginning of the study plus follicle-stimulating hormone levels higher than 35 IU/L; age between 42 and 58 years; no use of any medication known to interfere with hormonal, glucose, or lipoprotein levels in the past 3 months; no use of steroidal or nonsteroidal anti-inflammatory drugs in the last 15 days. Patients with diabetes, previous hysterectomy, endometrial thickness >0.5 cm, history of cancer, thromboembolism, or established cardiovascular disease were excluded [11]. Approval for this study was obtained from the Institutional Review Board and the local Ethics Committee, and written informed consent was obtained from every subject. The study was registered at clinicaltrials.gov (NCT01432028).

2.2. Study protocol

The sample has been partially described in a previous crossover randomized study [11] focusing on the effects of low-dose oral HT and non-oral HT on endothelial function markers and metabolic variables in early postmenopausal women. Briefly, women were randomized to receive non-oral HT (3 mg/day intranasal estradiol daily or 1.5 mg/day transdermal estradiol and 200 mg/day vaginal micronized progesterone for 14 days/month) or low-dose oral HT (oral estradiol 1 mg and drospirenone 2 mg/day) for 3 months. Then the two groups were crossed over without washout for an additional 3 months. In the present study, the correlation between genotype and us-CRP, anthropometric and metabolic variables was evaluated before and after 6 months with both forms of HT considered together.

2.3. Anthropometric measurements

Anthropometric measurements included body weight, height, BMI (current kg/m^2) and waist circumference (waist measured at the midpoint between the lower rib margin and the iliac crest, perpendicularly to the long axis of the body, with the subject standing balanced on both feet, spread approximately 20 cm apart, with both arms hanging freely, WC) [12]. Blood pressure was measured after a 10 min rest. The same calibrated mercury manometer attached to a 12.5 cm × 23 cm inflatable cuff was used in all patients by the same operator. The fifth Korotkoff sound was adopted to determine diastolic blood pressure [13].

2.4. Laboratory measurements

Blood samples were collected before and after treatment. All samples were obtained between 08:00 and 10:00 a.m. After a 12-h overnight fast, blood samples were drawn from an antecubital vein for determination of lipid profile (total cholesterol, HDL cholesterol and triglycerides) plasma glucose (oral glucose tolerance test), and insulin. Blood samples were also drawn for us-CRP. LDL cholesterol was estimated indirectly with the Friedewald formula [14]. The LAP index was calculated using the formula [waist (cm) – 58] × triglyceride concentration (mmol/L) [10].

2.5. Biochemical and hormone assays

Total cholesterol, HDL cholesterol and triglycerides were determined by colorimetric-enzymatic methods (Bayer 1650 Advia System, Deerfield, USA), with intra- and inter-assay coefficients of variation (CV) <3%. Glucose was determined by the hexokinase method with intra-assay CV <3.4% and interassay CV <2.1%. Us-CRP concentrations were measured using a nephelometric method (Siemens Dade Behring, Deerfield, USA), with sensitivity of 0.17 mg/L and intra- and inter-assay CV <5%. Serum insulin levels were determined by electrochemiluminescent immunoassays (Roche Diagnostics) with sensitivity of 0.200 μIU/mL, intra-assay CV 2.0% and interassay CV 4.3%.

2.6. Genotyping

In addition to serum samples, whole blood samples were collected from all women. Genomic DNA was extracted from peripheral leukocytes following the technique described by Miller and associates [15]. The DNA samples were diluted to 2 ng/mL and genotyped for SNP rs9939609 T>A and rs8050136 A>C of the FTO gene by real-time polymerase chain reaction (7500 Fast Real-Time polymerase chain reaction Systems, Applied Biosystems, CA, USA), using the allelic discrimination assay with TaqMan MGB primers and probes (Applied Biosystems, CA, USA). For a final volume of 4 μL per sample, TaqMan Master mix (2.5 μL), TaqMAn assay (0.250 μL) and H_20 (1.250 μL) were added. For a total reaction volume of 5 μL, 1 μL of DNA was added. Reaction conditions for the SNP rs9939609 were: 95 °C (10 min) after 50 cycles of denaturation at 95 °C (15 s) and annealing at 61 °C (1 min). Reaction conditions for rs8050136 were: 95 °C (10 min) after 40 denaturation cycles at 95 °C (15 s) and annealing at 60 °C (1 min). Endpoint fluorescent readings were performed by 7500 Fast System Sequence Detection Software version 1.4.

We calculated Lewontin's D' ($|D'|$) r^2 between each pair of genetic markers for estimating the linkage disequilibrium [16,17]. Haplotypes were constructed from the combination of the two FTO polymorphisms (rs9939609 and rs8050136), and their frequencies were inferred using the PHASE 2.1.1 program [18]. The first letter of each haplotype refers to the rs8050136 polymorphism, and the second to the rs9939609 polymorphism.

2.7. Statistical analysis

Results are expressed as means ± SD or medians and interquartile range (25–75%). Analysis of variance for Latin square design

Table 1
Distribution of anthropometric and metabolic variables according the genotype of SNP rs9939609 in postmenopausal women before and 6 months after hormone therapy.

	T/T		T/A		A/A		*p*
	Baseline	6 months	Baseline	6 months	Baseline	6 months	
Waist circumference (cm)	84.7 ± 8.2	84.0 ± 8.1	83.3 ± 7.1	81.7 ± 7.3	84.7 ± 5.0	84.0 ± 3.9	0.42
Body mass index (kg/m^2)	26.6 ± 2.8	26.4 ± 2.8	25.9 ± 3.4	25.9 ± 3.6	25.8 ± 2.6	25.5 ± 2.2	0.51
Systolic blood pressure (mmHg)	119 ± 13	117 ± 13	117 ± 14	114 ± 14	122 ± 12	114 ± 14	0.41
BP (mmHg)	77 ± 6	76 ± 7	74 ± 8	74 ± 9	78 ± 3	75 ± 7	0.54
Fasting glucose (mg/dL)	93.1 ± 9.2	92.0 ± 7.2	88.7 ± 7.5	89.9 ± 7.85	100.0 ± 18.7	101.3 ± 13.9	0.37
Glucose at 120 min (mg/dL)	102.6 ± 22.4	102.8 ± 29.6	100.5 ± 27.7	110.9 ± 36.2	121.3 ± 36.8	138.3 ± 43.9	0.12
Fasting insulin (μUI/mL)	7.9 (5.8–10.4)	7.2 (5.5–11.8)	5.7 (4.2–8.7)	6.5 (4.7–9.3)	7.0 (6.2–9.4)	6.1 (4.8–7.4)	0.59
Serum cholesterol (mg/dL)	216.0 ± 33.6	193.7 ± 39.4	212.3 ± 27.6	196.9 ± 27.3	230.5 ± 20.0	216.3 ± 47.1	0.74
HDL-c (mg/dL)	63.8 ± 18.6	57.2 ± 16.8	62.5 ± 13.3	58.9 ± 12.0	63.5 ± 10.7	61.2 ± 14.9	0.28
LDL-c (mg/dL)	129.3 ± 31.9	119.6 ± 28.4	125.9 ± 24.9	112.2 ± 26.3	136.2 ± 21.5	129.6 ± 35.3	0.71
Serum triglycerides (mg/dL)	108.8 ± 52.3	115.3 ± 59.4	116.9 ± 51.0	127.6 ± 62.4	153.8 ± 52.3	122.1 ± 44.9	0.05
C reactive protein (mg/L)	1.2 (0.6–2.9)	1.4 (0.4–2.5)	1.5 (0.7–2.8)	2.1 (0.8–3.3)	2.1 (1.1–4.1)	1.2 (0.6–1.8)	0.19
Lipid accumulation product	28.8 (17.4–42.6)	29.5 (18.0–46.9)	29.3 (18.4–43.8)	26.7 (15.4–52.7)	49.9 (31.0–53.6)	32.9 (23.0–46.4)	0.03

Data are mean ± SD values median and interquartile range (25–75%) (ANOVA for repeated measures); *p* = interaction of HT and genotype, i.e. comparisons before and after 6 months of hormone treatment in each group and between genotype groups.

was used before joining the HT groups to assess time, treatment route and carryover effects. No carryover was observed for any variable. Non-normally distributed parameters were log10 transformed to approximate a normal distribution curve before statistical analysis. Differences between measurements at baseline and at follow-up were tested with ANOVA for repeated measures. Data were considered significant at $P < 0.05$.

All analyses were performed using the Statistical Package for the Social Sciences 18 (SPSS, Chicago, IL, USA).

3. Results

The mean age of participants was 51 ± 3 years. The mean time since menopause was 22 ± 10 months. Patients were mostly Caucasian (90.6%), with the remaining participants having mixed (African and European) descent. While BMI and glucose remained unchanged after HT, waist circumference, systolic blood pressure, total cholesterol, HDL-c and LDL-c were reduced after 6 months in the overall sample ($P < 0.05$).

Eighty-six patients were genotyped. The frequency of the SNP rs9939609 was 44.2% for the TT genotype, 40.7% for the TA genotype, and 10.5% for the AA genotype. The frequency of the SNP rs8050136 was 13.6% for the AA genotype, 35.8% for the AC genotype, and 50.6% for the CC genotype. These genotype frequencies are in agreement with Hardy–Weinberg equilibrium for both polymorphisms. The rs9939609 polymorphism was in almost complete linkage disequilibrium with the rs8050136 polymorphism ($|D'| = 0{\cdot}953$; $r^2 = 0.876$). Five haplotypes were inferred in this sample (Ht1: CTCT, Ht2: CTCA, Ht3: CTAA, Ht4: ATAA, Ht5: AAAA). Haplotype frequencies were 46.4% for Ht1, 42.7% for Ht2/Ht3/Ht4, and 10.9% for Ht5.

Table 1 shows the distribution of anthropometric and metabolic variables according to the genotypes of the SNP rs9939609 in postmenopausal women before and after HT. Most of the studied variables remained unchanged after HT, with the exception of LAP, which were lowered after HT in women with the AA genotype ($P = 0.03$).

Table 2 presents the distribution of anthropometric and metabolic variables according to the genotypes of the SNP rs8050136 in postmenopausal women before and after HT. No changes were found among genotypes in the studied variables.

Table 3 shows the distribution of anthropometric and metabolic variables according to haplotypes. Most of the studied variables remained unchanged after HT, with the exception of LAP, which decreased slightly after HT in women presenting haplotype Ht5.

4. Comments

In the present study, FTO gene polymorphisms were not associated with adverse changes in metabolic variables or us-CRP levels in response to HT in postmenopausal women. It is important to note, however, that because of our selection criteria, only women in the first 3 years of the menopause, without clinical evidence of disease, were included in the study. This may have prevented us from identifying an association between the investigated SNPs and altered metabolic variables such as total cholesterol, LDL-c and HDL-c, which reflect a pathologic phenotype.

To the best of our knowledge, this is the first study assessing the relationship between FTO gene polymorphisms and HT. In general, studies focusing specifically on the effect of HT in early postmenopausal women report favorable outcomes. For example, the Coronary Artery Calcium Study (WHI-CACS) [19], which included women with age between 50 and 59 years, reported that beginning HT soon after the menopause contributes to a reduction in coronary artery calcification and in the prevalence of subclinical coronary disease. A reanalysis of WHI data [20] showed that women starting HT near the menopause also present a reduction in the risk of developing cardiovascular disease. In addition, one meta-analysis of randomized clinical trials comparing the results of coronary heart disease after menopausal HT in young versus older women demonstrated a cardiovascular benefit of early HT initiation [21].

Our group has also observed that treatment did not affect variables related to cardiovascular risk in a population of healthy, early postmenopausal women in a study comparing low-dose oral HT and nonoral HT [11]. Similarly, in the present study, no changes were found after HT in the anthropometric and metabolic profile of postmenopausal women. These observations are supported by evidence suggesting that HT does not have adverse effects on BMI [22], blood pressure [23] and vascular function [24].

We observed a strong linkage disequilibrium, consistent with the findings of previous studies [25,26], between the two polymorphisms of the FTO gene. However, even though higher LAP values were recorded before treatment in women carrying genotype AA in either SNP or in the Ht 5 haplotype, which contains both A alleles of the two SNPs, no deleterious LAP changes occurred after treatment. Concerning the LAP index, results from the Ludwigshafen risk and cardiovascular health study (LURIC), which included postmenopausal women at high cardiovascular risk, have shown a positive association between high LAP and heart failure mortality in normal weight women [27]. Another study showed an independent association of LAP levels with

Table 2
Distribution of anthropometric and metabolic variables according to the genotype of SNP rs8050136 in postmenopausal women before and 6 months after hormone therapy.

	A/A		A/C		C/C		p
	Baseline	6 months	Baseline	6 months	Baseline	6 months	
n (%)	11 (13.6)	11 (13.6)	29 (35.8)	29 (35.8)	41 (50.6)	41 (50.6)	
Waist circumference (cm)	82.8 ± 6.2	81.9 ± 5.8	83.6 ± 7.2	82.0 ± 7.5	84.7 ± 7.9	84.0 ± 7.8	0.54
Body mass index (kg/m^2)	24.6 ± 3.5	24.4 ± 3.2	26.1 ± 3.2	26.06 ± 3.3	26.7 ± 2.8	26.5 ± 2.86	0.81
Systolic blood pressure (mmHg)	122 ± 12	114 ± 13	116 ± 14	113 ± 15	119 ± 12	117 ± 13	0.48
Diastolic blood pressure (mmHg)	77 ± 4	76 ± 6	74 ± 8	74 ± 9	76 ± 6	76 ± 7	0.95
Fasting Glucose (mg/dL)	97.0 ± 18.2	99.2 ± 13.4	88.4 ± 7.4	89.5 ± 8.1	93.0 ± 8.9	91 ± 7.1	0.23
Glucose at 120 min (mg/dL)	118.2 ± 33.8	134.7 ± 40.2	100.2 ± 30.5	111.8 ± 39.0	102.1 ± 21.6	101.8 ± 28.7	0.07
Fasting insulin (μUI/mL)	7.0 (5.4–9.0)	6.1 (4.7–7.2)	5.7 (4.2–9.1)	6.4 (4.4–9.5)	7.9 (5.8–10.2)	7.2 (5.4–10.3)	0.61
Serum cholesterol (mg/dL)	227.3 ± 19.8	212.0 ± 43.2	211.5 ± 29.8	195.6 ± 29.2	215.6 ± 32.3	195.0 ± 38.4	0.87
HDL-c (mg/dL)	60.4 ± 12.1	58.5 ± 14.8	63.9 ± 13.5	59.7 ± 12.3	64.0 ± 17.9	57.7 ± 16.3	0.35
LDL-c (mg/dL)	136.1 ± 19.9	126.4 ± 32.7	123.8 ± 26.4	109.6 ± 27.8	129.1 ± 30.5	120.6 ± 27.7	0.69
Serum triglycerides (mg/dL)	153.4 ± 47.8	131.1 ± 50.8	116.0 ± 53.1	129.5 ± 63.6	107.2 ± 51.1	111.9 ± 58.2	0.10
C reactive protein (mg/L)	2.1 (1.4–3.3)	1.2 (0.6–1.9)	1.2 (0.6–2.5)	2.1 (0.8–3.4)	1.3 (06–2.9)	1.4 (0.5–2.6)	0.07
Lipid accumulation product	40.9 (26.4–53.6)	32.9 (22.6–43.5)	30.6 (18.2–46.8)	32.7 (15.2–53.1)	27.7 (18.1–42.6)	27.6 (17.9–46.6)	0.10

Data are mean ± SD values median and interquartile range (25–75%) (ANOVA for repeated measures); p = interaction of HT and genotype, i.e. comparisons before and after 6 months of hormone treatment in each group and between genotype groups.

increased risk of incident cardiovascular disease among women but not men [28]. This is also in agreement with previous studies by our group that showed a relationship between LAP and cardiovascular risk factors [29] as well as with the AA genotypes of both FTO gene polymorphisms [8].

The mechanism of action of the FTO variant on risk of metabolic traits and markers of cardiovascular risk remains uncertain. Recent studies suggest that FTO is a member of the non-heme superfamily, which encodes 2-oxoglutarate (2-OG)-dependent dioxygenases [30]. Members of this superfamily are involved in various cellular processes, including DNA repair, fatty acid metabolism and post-translational modifications. The SNPs rs9939609 and rs8050136 are not likely a causal variant; SNPs in the first intron of the FTO gene are in linkage disequilibrium with each other and there is not one SNP which can be treated as tagSNP across all ethnicities [31]. It is unclear whether these variations influence FTO expression or splicing or act as regulatory elements.

Concerning ethnicity, one meta-analysis of studies regarding the FTO gene and SNPs rs9939609 and rs8050136 provided significant evidence of a modest increase in the risk of obesity in Caucasian and Asian samples [31]. Another meta-analysis including only Asians showed the same polymorphisms associated with obesity risk in these populations [32]. Nevertheless, ethnic-specific associations were not observed between FTO and metabolic variables in a case–control study with postmenopausal women [7]. Interestingly, a recent meta-analysis has shown that participants having the FTO risk allele in SNP rs9939609 may have the odds ratio for obesity attenuated by 27% if they are physically active [33], suggesting a possible influence of lifestyle on phenotype/genotype interactions.

Other FTO gene polymorphisms have been associated with increased insulin, glucose, cholesterol and triglyceride levels, as well as with lower HDL-cholesterol levels in several populations [34,35]. Similarly, a previous study carried out by our group including most of the participants in the present study found that the SNP rs9939609 was related to abnormal glucose levels, but not to other metabolic variables [8]. Further, after adjustment for BMI, other investigators did not observe an association with insulin, HOMA-β, glucose and HDL-c [32,36].

In the present study, addressing the impact of FTO gene polymorphisms on the response to HT, we found no deleterious influence of homozygous wild genotype (AA) in the SNP rs8050136 on us-CRP levels after HT in recent postmenopausal women. Conversely, other studies have associated FTO gene polymorphisms with increased levels of CRP and higher cardiovascular risk in white European [37], and postmenopausal women [8], while others did not observe this association. Nevertheless, no previous study has specifically addressed the influence of polymorphisms on the response to HT.

Table 3
Distribution of anthropometric and metabolic variables according to the haplotypes of fat mass and obesity-associated gene variants in postmenopausal women before and 6 months after hormone therapy.

	Ht 1		Ht 2–4		Ht 5		p
	Baseline	6 months	Baseline	6 months	Baseline	6 months	
Waist circumference (cm)	84.7 ± 8.2	84.0 ± 8.1	83.3 ± 7.1	81.7 ± 7.3	84.7 ± 5.0	84.0 ± 3.9	0.42
Body mass index (kg/m^2)	26.6 ± 2.8	26.4 ± 2.8	25.9 ± 3.4	25.9 ± 3.6	25.8 ± 2.6	25.5 ± 2.2	0.51
Systolic blood pressure (mmHg)	119.5 ± 13.0	117.6 ± 13.8	117.0 ± 14.1	114.6 ± 14.1	122.8 ± 114.8	114.8 ± 14.9	0.41
Diastolic blood pressure (mmHg)	77 ± 6	76 ± 7	74 ± 8	74 ± 9	78 ± 3	75 ± 7	0.54
Fasting glucose (mg/dL)	93.1 ± 9.2	92.0 ± 7.2	88.7 ± 7.5	89.9 ± 7.8	100.0 ± 18.7	101.3 ± 13.9	0.37
Glucose at 120 min (mg/dL)	102.6 ± 22.4	102.8 ± 29.6	100.5 ± 27.7	110.9 ± 36.2	121.3 ± 36.8	138.3 ± 43.9	0.12
Serum cholesterol (mg/dL)	216 ± 33	193 ± 39	212 ± 27	196 ± 27	230 ± 20	216 ± 47	0.74
HDL-c (mg/dL)	63 ± 18	57 ± 16	62 ± 13	58 ± 12	63 ± 10	61 ± 14	0.28
LDL-c (mg/dL)	129 ± 31	119 ± 28	125 ± 24	112 ± 26	136 ± 21	129 ± 35	0.71
Serum triglycerides (mg/dL)	108 ± 52	115 ± 59	116 ± 51	127 ± 62	153 ± 52	122 ± 44	0.05
C reactive protein (mg/L)	1.5 (0.5–2.8)	1.4 (0.4–2.6)	1.7 (0.6–3.3)	2.1 (0.8–3.3)	2.6 (1.0–4.6)	1.2 (0.6–1.8)	0.19
Lipid accumulation product index	28.8 (17.4–42.6)	29.5 (18.0–46.9)	29.3 (18.4–43.8)	26.7 (15.4–52.7)	49.9 (31.0–53.6)	32.9 (23.0–46.4)	0.03

Data are mean ± SD values median and interquartile range (25–75%) (ANOVA for repeated measures); p = interaction of HT and haplotype, i.e. comparisons before and after 6 months of hormone treatment in each group and between haplotype groups.

Conclusions

The presence of fat mass and obesity-associated gene risk variants in healthy early postmenopausal women does not adversely affect their response of to hormone therapy.

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